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PORTRAIT

From vaccines to global health to vaccines

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In the days of my rebellious adolescence, I decided that never ever would I study medicine and work in health. In my family there were already too many doctors, notwithstanding the fact that my two younger brothers later went on and also embraced the medical profession… Why was that? A rejection of the establishment, of the paternalistic doctor-patient relationship? A reflection of my time? I was 13 in May 1968, a cultural and social turning point in French history, with student protests against capitalism and traditional values and institutions. Still, having spent my childhood with parents who devoted their life working in hospitals to save or improve the health of their fellow citizens, I felt strongly that I ought to contribute to society.

Having turned my back on medicine, I decided to become an agronomist in order to teach modern agricultural practices to farmers in sub-Saharan Africa. Arrogance or naivety? Either way, this did not work out, as ORSTOM – the predecessor to the French IRD (Institut de Recherche pour le Développement – was not interested in recruiting young women in a profession considered at that time as better suited for men.

I ended up specialising in biological engineering during my third year at the Ecole Nationale d'Agronomie in Montpellier, a vibrant student city in Southern France. After my PhD, I started my long journey back to where I had decided I would never go: health!

In 1980, Pierre Chambon (IGBMC, France) and Philippe Kourilsky (Institut Pasteur, France) supported the creation of what was the first biotechnology start-up in France: Transgene S.A. Under the leadership of the first scientific director of the company (Jean-Pierre Lecocq) I was in charge, with a few other youngsters from all over the world, of leveraging the power of the emerging molecular biology theories and tools to create the future.

Through sheer luck, my first project focused on the development of a recombinant vaccine against rabies. Glycoprotein G of the rabies virus is the only viral antigen recognized by anti-rabies neutralizing antibodies. Such antibodies, induced by conventional anti-rabies vaccines, are considered to be the main effectors of protection against the disease. Protein G is therefore a preferred target for the development of a recombinant vaccine against rabies. In the early 1980s, two US-based research teams, led by Enzo Paoletti (NY State Department of Health, Albany, USA) and Bernie Moss (NIH, USA), pioneered the use of recombinant vaccinia viruses as candidate vaccines for humans and animals. Several reasons justified the use of vaccinia virus as a vaccine vector: this virus had indeed demonstrated remarkable efficacy for the eradication of smallpox and it was hoped that similar success would be achieved for other infectious diseases for which genes corresponding to antigens with an immunizing power were available. In addition, the size and plasticity of the viral genome, as well as the presence of many non-essential genes for in vitro replication, made it possible to consider the integration of several genes encoding different antigens into a single virus, hence the possibility of producing polyvalent vaccines from a single recombinant virus. In collaboration with Robert Drillien and Danièle Spehner (Inserm, France), I started to construct recombinant vaccinia viruses[1] expressing rabies G. After a few failed attempts, finally the success: the recombinant vaccinia virus (commercialized later by Merial under the brand name Raboral as oral vaccine baits) demonstrated full protection of laboratory animals in 1981 and in foxes in 1986[2]. Since 1987, more than 250 million doses of Raboral were released into the environment to immunize wildlife against rabies. Large-scale use of Raboral has contributed to the elimination of wildlife rabies in Europe and in parts of the USA where it was used.

This success gave me a passion for research aimed at improving human or animal health in general and the prophylaxis of infectious diseases in particular. It also steered my career towards vaccine development and my next projects concentrated on the development of prototype vaccines against HIV and cancer, as described below.

In 1984, I took the responsibility for a collaboration between Transgene S.A. and Institut Pasteur (France) and Pasteur-Vaccines (now Sanofi-Pasteur) aiming at the development of a vaccine against HIV. I expressed most of the genes of the HIV-1, HIV-2 and SIV viruses in various host-vector systems (vaccinia virus, CHO cells, baculovirus, S. cerevisiae, E. coli), and purified and characterized corresponding proteins to produce prototype vaccines that were tested in animal models, including primates. The hybrid structure[3] of the env glycoprotein which I designed was part of the canarypox (ALVAC HIV) candidate vaccine tested in RV144[4], known as the Thai prime-boost AIDS vaccine trial. This large HIV vaccine trial evaluated in over 16,000 participants the efficacy of a vaccine regimen consisting of two candidates, ALVAC HIV and a recombinant purified HIV-1 gp120 (AIDSVAX B/E). The trial results, published in 2009, showed that the vaccine regimen reduced HIV risk by approximately 30 percent.

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To this date, Transgene S.A is still conducting clinical research on cancer immunotherapy targeting mainly breast and cervical cancers with encouraging results, based on prototype vaccines developed under my supervision.

After nearly 20 years in the biotech industry, I decided in 1998 to go back to academia, as a director of research at Inserm, the French Institut national de la santé et de la recherche médicale, where I started a research project on Hepatitis C, which included the search of a preventive vaccine. During that time, I also served as temporary advisor at the Special Programme for Research and Training in Tropical Diseases, hosted by the World Health Organization in Geneva (Switzerland), focusing on the development of vaccines against malaria, leishmaniasis and schistosomiasis, three important infectious diseases of poverty. I became very interested by the steward work of multinational organisations and decided in 2001 to spend a couple of years in Geneva after many years spent at the bench. What was initially meant to be a short stay ended up constituting a significant part of my scientific career. From 2001 to 2010, I was the Director of the WHO Initiative for Vaccine Research. The disease portfolio of the Initiative included tropical diseases, HIV/AIDS, tuberculosis, malaria, meningitis, respiratory diseases, diarrhoeal diseases, Japanese encephalitis, cervical cancer and measles. We conducted and coordinated activities related to product research and development and implementation research for vaccines and delivery devices. Achievements of the Initiative during that period included the development and large-scale introduction of a new conjugate Meningitis A[5] vaccine (in collaboration with Marc LaForce at PATH and Serum Institute of India, Ltd) throughout the African Meningitis Belt, and the development of a measles aerosol vaccine. I also initiated an ambitious programme of transfer of technology[6] for influenza vaccine production, which lasted from 2006 to 2018 and allowed several low- and middle-income countries to acquire the capacity to produce influenza vaccine domestically. During the 2009–2010 H1N1 influenza pandemic I was in charge of the WHO pandemic vaccine deployment initiative, which pioneered the delivery of 77 million doses of vaccine to 78 low- and middle-income countries to allow immunization of health workers and priority populations.

From 2010 to 2017 I was Assistant Director-General for Health Systems and Innovation at WHO, where my main responsibility was to support the 194 WHO Member States progressing towards universal health coverage. This work included engaging with policy-makers, global health partners, civil society, the academic world and the private sector, with a mission to: 1. provide information and evidence on health-related matters; 2. support countries developing, implementing and monitoring solid national health policies, strategies and plans; 3. support countries to assure the availability of integrated people-centred health services at an affordable price; 4. promote access to affordable, safe and effective medicines and health technologies, and; 5. promote research leading to high-quality evidence and innovative health-related technologies.

During 2014 and 2015 an outbreak of Ebola deemed a Public Health Emergency of International Concern affected a number of West African countries, and in particular Guinea, Liberia and Sierra Leone. The outbreak underscored the urgent need for a vaccine against Ebola and I had the honour of leading on behalf of WHO an unprecedented collaborative effort to accelerate the development of candidate Ebola vaccines which could immediately enter clinical evaluation. In August 2014, the government of Canada donated to WHO 800 vials of the vesicular stomatitis virus (VSV) – Zaire Ebola virus vaccine candidate (rVSV-ZEBOV) and by September 2014, WHO had organized a consortium (VEBCON) to conduct phase 1-trials in Geneva (Switzerland), Hamburg (Germany), Kilifi (Kenya) and Lambarene (Gabon) with financial support from the Wellcome Trust. Based on the data from these studies and others conducted in North-America, the appropriate dose of rVSV-ZEBOV for phase 3 efficacy studies could be determined in December 2014. In October 2014, it appeared that partnerships had been set up between US-NIH and the Liberian government as well as between US-CDC and the government of Sierra Leone to conduct Ebola vaccine efficacy trials in these two countries, but that there was no plan to evaluate the efficacy of any of the two more advanced vaccines (rVSV-ZEBOV from Merck and ChimpAd-ZEBOV from GSK) in Guinea. The Guinea vaccine Consortium was created to fill this void. The Consortium designed a novel cluster trial design called "ring vaccination" where contacts and contacts-of-contacts of a newly discovered Ebola patient were vaccinated. Rings were randomized to receive vaccination either immediately or after 21 days. The high-level efficacy[7] of the vaccine was demonstrated following observation that significantly more people contracted Ebola in the delayed rings as compared to the rings vaccinated immediately. Interim results were published as soon as August 2015, for a trial initiated in March of the same year. I represented WHO as the sponsor of the study, which was implemented by the Ministry of Health of Guinea, WHO, Médecins sans Frontières (MSF), Epicentre and the Norwegian Institute of Public Health. The trial was funded by WHO with support from the Wellcome Trust and the Governments of the United Kingdom, Norway and Canada, and MSF.

In order to build a safer world, based on the lessons learnt during the West-African Ebola epidemic, I led between 2015 and 2017 the development and early implementation of the WHO R&D Blueprint, a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crises.

Finally, serendipity has brought me home, and I realize that I have spent my life working on health, and mostly on vaccines. I have brought that passion with me as I left WHO in 2017 to return to a position of Director of Research at Inserm.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author.

Notes on contributor

About ***Marie-Paule Kieny***. Dr. Kieny is Director of Research at Inserm (Institut national de la santé et de la recherche médicale) in Paris, where she assists the President on International Institutional Collaborations. She is also the Chairman of the Board of the Drugs for Neglected Diseases Initiative (DNDi, Geneva, Switzerland) and of the Medicines Patent Pool Foundation (MPPF, Geneva, Switzerland) since July and August 2017, respectively, a member of the Board of the Human Vaccine Project (HVP, New York, USA), and a Non-Executive Independent Director of bioMérieux (Lyon, France).

Until June 2017, Dr. Kieny served as the Assistant Director-General for Health Systems and Innovation at the World Health Organization. Dr. Kieny directed the WHO Initiative for Vaccine Research from 2001 to 2010. Key successes under her leadership roles at WHO include coordinating the WHO R&D efforts during the 2014-2016 West-African Ebola epidemic and overseeing the successful implementation of a Phase III efficacy trial of an Ebola vaccine candidate in Guinea. She conceptualized and initiated the WHO R&D Blueprint, a global preparedness plan against emerging disease epidemics. She also participated in developing and introducing in sub-Saharan Africa a new vaccine against bacterial meningitis, addressing global supply of pandemic influenza vaccine especially in developing countries through technology transfer and manufacturing, and supporting developing countries strengthening their health systems towards Universal Health Coverage. Such initiatives are continuing priorities of Dr. Kieny.Before joining WHO, Dr. Kieny held top research positions in the public and private sectors in France, which included Assistant Scientific Director of Transgene S.A. from 1981 to 1988 and Director of Research and Head of the Hepatitis C Virus Molecular Virology Group at the Institute of Virology, (INSERM) from 1999 to 2000.

Dr. Kieny received her PhD in Microbiology (1980) and University Diploma in Economics from the University of Montpelier; Diplôme d'Habilitation à Diriger des Recherches from the University of Strasbourg in 1995. She has published over 350 articles and reviews, mainly in the areas of infectious diseases, immunology, vaccinology and health systems.

Dr. Kieny has been awarded the title of Chevalier dans l'Ordre National de la Légion d'honneur (Knight in the National Order of the Legion of Honour, France) in 2016, and of Chevalier de l'Ordre National du Mérite, au titre du Ministère de la Recherche (Knight of the National Order of Merit, under the Ministry of Research, France) in 2000. She was the recipient of the International Inserm Prize in 2017, the Génération 2000-Impact Médecin Prize in 1994, and the Innovation Rhône-Poulenc Prize in 1991.

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